PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Statin use and clinical outcomes in older men: a prospective population-based study
AUTHORS	Gnjidic, Danijela; Le Couteur, David; Blyth, Fiona; Travison, Thomas; Rogers, Kris; Naganathan, Vasi; Cumming, Robert; Waite, Louise; Seibel, Markus; Handelsman, David; McLachlan, Andrew; Hilmer, Sarah

VERSION 1 - REVIEW

REVIEWER	Arduino A Mangoni, Professor of Medicine of Old Age, University of Aberdeen, United Kingdom No competing interests declared.
REVIEW RETURNED	26-Nov-2012

THE STUDY	The study mainly involves community-dwelling older individuals at the healthier range of the spectrum. A relatively small group was frail at baseline. This should be discussed further as the results suggest a safety signal in this group.
RESULTS & CONCLUSIONS	The clear trend towards increased risk of institutionalisation in frail patients on statins vs. no statins warrants further discussion and interpretation.
GENERAL COMMENTS	The study addresses an important question and the results are well presented. Some points regarding data interpretation need to be further emphasised/discussed: - The population studied (community-dwelling older men) is at the 'healthier' end of the spectrum. While frail(er) subjects are also included they are a relatively small proportion. Further emphasis in the discussion should be given on the need to focus also on this subgroup because of some signals in the results as below. - Albeit no significant interaction was detected between frailty and statin use on institutionalisation rates, there was a clear trend as the HR in statin users was more than double (4.34) than non-users (2.07). While this group was relatively small, this potential signal warrants further appropriately powered studies. - In the whole group there is also a strong trend towards incresed risk of institutionalisation (CI 0.98-2.63). It may well be that a

	significant trend could be detected in a larger study. - As far as I understand data on statin use was only available at baseline. I think this should be further emphasised as a limitation in the discussion as we don't know whether statins were stopped, started, or their dose changed during the follow-up. Minor points: - I'm not sure the study Ref 15 was conducted in disabled women as it specifically targeted non-frail people.

REVIEWER	Yana Vinogradova Research Statistician University of Nottingham United Kingdom no competing interests
REVIEW RETURNED	26-Dec-2012

THE STUDY	Categorisation of duration of statin use as ≤3y and ≥4 years is not entirely logical – how, for example, is 3.5 years of statin use categorised? It would be clearer to report levels of statin use as proportions within the subgroup of statin users – rather than over the whole group. The original recruitment rate was 53.7%. It would be useful for the authors to comment on possible volunteer bias. Ref.1 is not really relevant as the prevalence of statin use in that paper was assessed in patients with renovascular disease, not in a general population. Page 12 lines 38-51 should be reworded to clarify that both for CVD diseases and reported comorbidities, the number of such diseases was dichotomised at the upper quartile. The participants were interviewed every 2 years and the data contain information on statin use and all confounders at each visit. The authors, however, investigate the effect of statin use only at the baseline – ignoring possible changes in participants' health state, habits and, therefore, drug consumption which might have occurred during the more than 6 years of follow-up. According to unpublished data for up to 2008 from QResearch, and particularly relating to the older population, use of statins was growing during the study years so doctors might have started prescribing statins simply because they had been convinced of their benefits. Similar trends were observed in a Danish study, which also noted a decrease in use for 2009 (Wallach Kildemoes 2012, Health Policy, 108, 216-27). This information might be taken into account by applying the Cox model with time-dependent covariates and so increase the credibility of the results. Did the authors consider it? If not, the reasons should be discussed. According to the description

	of the study in ref. 19, the first follow-up clinical visit was to be funded. Did the authors run any comparative analysis (e.g. sensitivity) based on this first follow-up visit? Again, any reason for not doing so should perhaps be mentioned.
RESULTS & CONCLUSIONS	As the authors note in the discussion there are no studies investigating the association between statin use and institutionalisation. But nothing is said about studies looking at the association between mortality and statin use. There are observational studies based not on general population data but on particular groups from a general population with common old age conditions. These should be mentioned in Discussion.

REVIEWER	Golomb, Beatrice University of California San Diego, Medicine
REVIEW RETURNED	17-Jan-2013

GENERAL COMMENTS	The study addresses a very important issue. The important findings should be better highlighted, and placed better into context of existing literature. You might consider emphasizing institutionalization, the element that has not been looked at in the elderly, and using the mortality findings as a comparator to available RCT data to identify potential net direction of bias. Major issues: 1. Central Findings a. It is unclear why the vital finding that medium and high dose statin users had significantly increased rates of institutionalization is buried (not mentioned in abstract or conclusions). In general, healthy user/ healthy tolerator effects of statins have shown greater spurious advantages with high dose statin use (not supported in head to head higher vs lower dose comparisons in RCTs, even in stable CAD)[Golomb, 2009 #54142]. b. It is emphasized (1st sentence of discussion) that "The objective of this cohort analysis was to evaluate the relationship between statins and two clinically important outcomes, institutionalisation and death in older men, accounting for frailty." It was also stated that elderly respond worse to drugs – i.e. frailty is a potential effect modifier. Given these, an anaysis stratified on frailty is the most sensible. A range of analyses comparing frail on statin to nonfrail not on statin (which are uninterpretable) are included; while the hazard ratio and CI comparing frail on-statin to frail not on statin is not. This analysis is central to the purpose of the study. (It appears, from dividing taking the ratio of HRs relative to healthy not-on-statin persons, that the HR for institutionalization with statins, among frail individuals, would be about 2.1) Relation of statin use to institutionalization in frail elderly is important to frail elderly, whether or not the frailty x statin interaction achieves significance here.

	Healthy User Effects: The study design bears the expected major limitation for cohort studies of preventive medications. You correctly mention that users are more likely to have CAD (which may be controlled for – or stratified on). Healthy user bias is alluded to briefly, but the power of this effect in observational studies of preventive medications is powerful: this led HRT to appear to have strikingly large and significant benefits to incident dementia and CVD. Subsequent randomized trials, ensuring against systematic differences between HRT users and nonusers (other than HRT use), showed the causal effect of HRT was modest but significant increase in these outcomes. Etc. Similar problems have arisen flu vaccine and statin trials. An editorial in BMJ has reviewed the foundations for these forms of bias in relation to statin use (including healthy tolerator effects, also strongly germane here)[Golomb, 2011 #67608]. Though it is alluded to in the discussion, this limitation might be more explicitly acknowledged as a potential large force. 2. Management of other forms of bias and confounding: a. Covariates/ confounders vs mediators "Other medical conditions included: diabetes, thyroid dysfunction, osteoporosis, Paget's disease, stroke (cause), Parkinson's disease (consequence), epilepsy, intermittent claudication (Cause), chronic obstructive lung disease, liver disease, chronic kidney disease or renal failure, cancer (excluding non-melanoma skin cancers), or arthritis. The number of reported comorbidities was dichotomised at the upper quartile (≤1 versus ≥2). Data on body mass index (BMI; kg/m2) was obtained. Multiple medication use or polypharmacy was defined as the use of ≥5 regular prescription medicines" Comment: Several of these may be caused by statins* and serve as mediators of mortality, or correlate with processes that are involved in mediation. Adjusting for potential mediators (or for factors correlated with and thus collinear with such mediators) may "adjust out" a true association. At the very minimum, this should be characterized as a limitation of the study. ** diabetes (particularly in elderly), cancer (RCT evidence is exclusively in elderly), liver disease, kidney disease, presumed "intermittent claudication" as a manifestation of statin exercise intolerance (I was involved in care of a patient with documented PAD (ABI ~0.6 bilaterally) and presumed IC manifested by months of severe calf pain with ambulation arising at < 1 block, who had been pre-opped and was scheduled for vascular surgery. He stopped his statin prior to the surgery and the symptoms calf pain with ambulation fully resolved, with no restriction in ambulation, and did not recur (he remained off statins).} A number of the health variables that have been adjusted are outcomes to which statin use can predispose, particularly in elderly. {These include diabetes (particularly in elderly)[Sattar, 2010 #56915][Golomb, 2012 #67719]. higher BMI, neurodegenerative

	disease, cancer (in elderly exclusively[Shepherd, 2002 #4295].), renal and liver disease.} An adjustment approach that includes adjustment for potential mediators, or factors correlated to mediators, is problematic, it may "adjust out" a true relationship. Similarly, statins can promote polypharmacy to treat adverse effects, which may be mediators in statin induced death and institutionalization. (I had a striking recent case of a patient who was out of town for six months, during which a doctor initiated statins, which led to a cascade of problems, causing the patient to be placed on more medications for problems, and to develop more problems from the medications. These all resolved when I stopped the set of six or seven added medications.) There is not a foolproof way of addressing these, because these problems can also arise in absence of statin use, and in that fraction adjustment would be beneficial. Healthy tolerator bias: some who are not on statins may select into the nonuser group via statin intolerance – which may be tied to lower vigor (e.g. greater mitochondrial dysfunction[Golomb, 2008 #51302]), which may predict worse outcomes. It may also lead to loss of evidence of dose effects (higher doses are more likely to lead to discontinuation, and further boosting of lower vigor participants into the nonuser group Recommendation: This limitation should be acknowledged. 3. Power: Bias and confounding add significant uncertainty to how meaningful the point estimates are. But supposing they were presumed credible, effects of the observed magnitude (particularly for institutionalization) would be important to identify. Failure for effects of this magnitude to provide significance emphasizes that the study is underpowered. (It should probably not be characterized as a large study: for a cohort study, it is rather small.) 4. Statements needing revision: Finally, a number of statements and characterizations are in need of correction or revision a. Introduction: "While the data from published RCTs and prospective studies indicate that statins reduce the incidence of cardiovascular events and all-cause mortality there are still significant gaps in evidence on the safety of statins in a real-world setting." Comment: There was NOT reduction in all-cause mortality in the only randomized trial focused on the elderly (the PROSPER trial)[Shepherd, 2002 #4295]. Nor was there even a trend to mortality benefit with statins relative to placebo (odds ratio approximating 1.0), though this was a high-CVD risk sample, with heart disease or risk factors beyond high cholesterol – a sample far more likely a priori to experience mortality benefit than the sample here, with greater expected statin benefits and fewer expected harms. Moreover, that trial showed a statistically significant 25% increase in incident cancer[Shepherd, 2002 #4295] (a finding that was elsewhere shown to be modified significantly with age, and

	which is completely absent in samples of middle aged subjects, and meta-analyses of these. Papers reviewing separate risk-benefit considerations of statin use in elderly are available[Golomb, 2005 #9692]. b. Statement under "Article focus": "There is limited data in relation to statin use and clinical outcomes in representative populations of community-dwelling older people." Comment: This implies these are data in "representative populations of community-dwelling older people." BMJ Open just published a study showing that elderly who participate in studies are healthier[Golomb, 2012 #77145]. Subjects here were already participants in a program, who are expected to have been healthier than their age-sex matched compatriots, at least at the time of initial entry, a limitation that should be acknowledged, at least by indicating. There is little cause to presume this sample is much more representative than the clinical trial sample in PROSPER, which has the advantages of randomization and larger sample size[Shepherd, 2002 #4295]. c. Statement under "Key messages": "The findings of this prospective cohort study imply no independent association between statin use and institutionalisation or death in community-dwelling older men." Comment: "Imply no independent association" implies absence of an independent association. The findings do not do this. They suggest the possibility of a sizable link to institutionalization, particularly in frail elderly, despite potential sources of confounding most of which will work against an association, but the study is underpowered to demonstrate significance. (A more correct statement is that the findings indicate need for further study, but can neither affirm nor exclude an important, sizeable effect on institutionalization.) The trend to lower HR for death in statin users is well within the range that may be ascribed to healthy user / healthy tolerator effects noted above. But the findings for institutionalization are both sizeable and opposed in direction to expected healthy user effects. The HR for institutionalization for statin users was 2.1 fold greater than for nonstatin users (4.3 / 2.07) = 2.1. Doubling in the risk of institutionalization, if affirmed in a larger study, would be an extraordinarily important finding. This has serious prospects to be real, given randomized data showing fatigue (which you cite), increased glucose problems which have been found to be markedly stronger in trials with more older participants[Sattar, 2010 #56915]; and within trials, among subjects of older age within the elderly age group[Golomb, 2012 #67719]. (Diabetes will in turn lead to prospects for mortality and disability, and also to more medications with their own prospects for morbidity), increased weakness in elderly (in RCT settings). Recommendation: The statement should to be revised. The text should make clear that a) no significant finding was observed

	(absence of significance is not evidence of absence in the setting of a large hazard ratio); b) that well documented healthy user effects, documented for numerous preventive medications (flu vaccine, HRT) extending to statins could lead to bias in a favorable direction; c) that if the observed point estimate, of a doubling in risk of institutionalization among frail persons (and a 40% increase among others) is real, it would be important to demonstrate, or refute, in subsequent study. d. Statement: "Randomised trials in frail and robust older people with clinically relevant endpoints are required to inform therapy in this population" Reviewer Comment: Such study in (generally) robust elderly – i.e. the elderly that are generally able to participate in studies[Golomb, 2012 #77145] -- already showed no (trend toward) mortality or serious morbidity benefit, complete loss of the stroke benefit seen in younger age, and a statistically significant increase in incident cancer. Institutionalization has not been examined, but the available evidence does not provide significant support for use of statins in elderly, even if robust providing lower prospects for harm, and at higher than typical prospects for benefit (with (stable) CAD). Frail elderly inherently don't tend to show up for studies[Golomb, 2012 #77145]. Cognitive limitations (which also affect compliance), physical frailty, transportation obstacles, and vigor all likely play roles. If some were to qualify by some definition of frailty, they would likely still be highly different from the frail group they are intended to reflect Recommendation: Be clear what exactly you want these randomized trials to do, that a) they are capable of doing (so, frail elderly unlikely to be able to participate in a RCT); and b) have not already done. Under "Strengths and limitations of this study" e. Far more important than either the first statement (saying this is a large study -- which for a population cohort it is not); or the 2nd focusing on geography, is the limitation that this study is underpowered even to show significance of a doubling in institutionalization among the frail group, and a 40% increase in the healthy group. f. "the possibility of confounding by indication and unmeasured confounders cannot be excluded." In addition to confounding by indication and by "unmeasured" confounders, is the influence of measured variables for which adjustment may adjust out mediating mechanisms. I would rephrase this limitation and perhaps emphasize that observational studies of preventive medication users, including statins, have often been biased by healthy user and healthy tolerator bias[Golomb, 2011 #67608]. Introduction g. However, it is not clear how the findings of these trials translate

	to clinically significant outcomes in general populations of older people. This may be because the representation and representativeness of older people in published RCTs of statins is generally poor.5 Comment: You are the one drawing the inference that it is not clear how findings of trials translate, from which the readers infer that you have a reason. Therefore it isn't meaningful to say "This may be because". (Representativeness of others' criticized: should acknowledge limitations in representativeness here.) Competency: Statement: All participants were screened for cognitive impairment, and those who tested positive underwent full neuropsychological assessment. Participants were classified as cognitively impaired if they were diagnosed with either dementia or mild cognitive impairment" Query: Were they administered MacArthur competency testing or some other procedure, to ensure those who were cognitively impaired had competency to consent? Prior Statin Use How was prior statin use handled? Adverse effects of statins on muscle, neuropathy, and cognition can have lingering pathological and sometimes clinical effects; failure to address this can produce bias to the null, for effects that are adverse. Citation needed: Frail individuals are more likely to use more medicines,10 and are at increased risk of adverse effects from medicines." Comment: This is a major reason behind your stratified analysis, a citation should be provided. Clarification needed: Statement: "Participants were asked whether they had taken any subsidised prescription or non-prescription medications during the past month." Clarification sought:: Why just subsidized medications? Clarification needed: "Data on the duration of statin use (years) were obtained" How? If you could obtain duration, you could obtain prior statin use Clarification needed: What was the average follow-up period? You mention the maximum follow-up of ~6.8 years. Clarification needed:

	"Statistical Analysis: Data are summarised as means (standard deviations) or counts (proportions). Differences between statin users and non-users were compared using the non-parametric or χ2-tests as appropriate…" Comment: Presumably you are referring to covariates rather than outcomes: if so, so clarify. Clarification needed: "We then conducted the Cox proportional hazards regression models for the effects of statins on institutionalisation and death, adjusted for all potential confounding factors at baseline." Please clarify the exact list of variables that were adjusted and how each were defined/ rated. Important statement: "It is unknown whether medicines do more good than harm in older adults with established geriatric syndromes." This is an important comment, but I wonder if you may wish to qualify if (e.g., preventive medications). "harm" and "good" may be unclearly defined, and medicines that reduce suffering may be considered by some to clearly do good (even if they were to increase mortality) Discussion "These findings suggest that statins in frail older men may not reduce the risk of institutionalisation or death." In fact, your study found an increase in institutionalization, particularly with higher statin doses. Strengths section " good quality medication and outcome data" In what way are the medication data good quality? They aren't from an electronic database; and you don't seem to address prior statin use… " and adjustment for a number of covariates related to the risk of institutionalisation and death." Unfortunately, some may be in the causal pathway. The propensity score is problematic due to the cause/ covariate/ confounder/ mediator issue that affects a number of the covariates. "In relation to statin exposure, non-users group may include former users of statins." That nontolerators may be unhealthier and disproportionately populate the nonuser group with sick people is especially likely to be a big factor among elderly. Concluding paragraph "In this prospective observational study, use of statins was not

	associated with increased risk of institutionalisation or death. However, in this sample, frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure." The latter sentence is both unrelated to the described intent of the study and is a "duh". Why is this statement included, but the study-relevant finding of significant increased institutionalization among those on higher statin doses not mentioned here?* Why is the doubling of institutionalization for statin users, among frail elderly, not mentioned here (or in the results)? *"Medium (HR=2.00; 95%CI: 1.02 to 3.93) and high (HR=2.45; 95%CI: 1.12 to 5.33) dose statin users were significantly more likely to be institutionalised when compared to those not taking statins."

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Arduino A Mangoni, Professor of Medicine of Old Age, University of Aberdeen, United Kingdom

No competing interests declared.

1) The study mainly involves community-dwelling older individuals at the healthier range of the spectrum. A relatively small group was frail at baseline. This should be discussed further as the results suggest a safety signal in this group.

Thank you. We have addressed this and added the following statement (page 20):

Studies with larger number of frail participants are needed to estimate the risks of statins in frail older people.

2) The clear trend towards increased risk of institutionalisation in frail patients on statins vs. no statins warrants further discussion and interpretation.

We have addressed this in the discussion section (page 20). The following statement was added:

Even though there was no significant interaction between statin use and frailty on institutionalisation rates, frail men using statins had twice the risk of institutionalisation as frail men not using statins.

The study addresses an important question and the results are well presented. Some points regarding data interpretation need to be further emphasised/discussed:

3) The population studied (community-dwelling older men) is at the 'healthier' end of the spectrum. While frail(er) subjects are also included they are a relatively small proportion. Further emphasis in the discussion should be given on the need to focus also on this subgroup because of some signals in the results as below.

Thank you. We have addressed this as per comment one (please see page 20).

4) Albeit no significant interaction was detected between frailty and statin use on institutionalisation rates, there was a clear trend as the HR in statin users was more than double (4.34) than non-users (2.07). While this group was relatively small, this potential signal warrants further appropriately powered studies.

We have discussed the implications of these analyses in more detail, and have highlighted the need for future studies to confirm these findings (pages 19-20).

5) In the whole group there is also a strong trend towards increased risk of institutionalisation (CI 0.98-2.63). It may well be that a significant trend could be detected in a larger study.

Thank you. We have now stated the following (page 19):

In our study, statin users had a hazard ratio of 1.60 (95%CI: 0.98 to 2.63) for increased risk of institutionalisation. Future studies conducted in larger populations are needed to investigate associations between statins and institutionalisation in older people.

6) As far as I understand data on statin use was only available at baseline. I think this should be further emphasised as a limitation in the discussion as we don't know whether statins were stopped, started, or their dose changed during the follow-up.

For these analyses, data on statins use was available at baseline only. In addition, we were unable to differentiate former users from non-users, as discussed on page 21.

We have now added the following sentence on page 21;

“Moreover, it is unknown whether statins were stopped, started or the dose was changed during the follow-up”.

7) Minor points:

- I'm not sure the study Ref 15 was conducted in disabled women as it specifically targeted non-frail people.

Thank you. We have corrected this (page 10).

Reviewer 2: Yana Vinogradova, Research Statistician, University of Nottingham, United Kingdom

No competing interests

1) Categorisation of duration of statin use as ≤3y and ≥4 years is not entirely logical – how, for example, is 3.5 years of statin use categorised?

Thank you for pointing this out. Duration of statin use was categorised as <4 and ≥4 years. We have now corrected this typographical error throughout the paper (pages 12, 17 and Tables 2-3).

2) It would be clearer to report levels of statin use as proportions within the subgroup of statin users – rather than over the whole group.

Data for the whole population and according to statin use has been tabulated in Table 1. The proportions within statin users and non-users have been reported. We have now clarified this in a table footnote (page 25).

3) The original recruitment rate was 53.7%. It would be useful for the authors to comment on possible volunteer bias.

Thank you. We have added the following text (page 21):

Participation in the CHAMP study was voluntary and clinical characteristics of participants may have differed to those of non-participants, which may have biased the sample.

4) Ref.1 is not really relevant as the prevalence of statin use in that paper was assessed in patients with renovascular disease, not in a general population.

We have deleted this reference, and the sentence on page 1 related to this reference.

5) Page 12 lines 38-51 should be reworded to clarify that both for CVD diseases and reported comorbidities, the number of such diseases was dichotomised at the upper quartile.

Thank you. We have amended this section as suggested.

6) The participants were interviewed every 2 years and the data contain information on statin use and all confounders at each visit. The authors, however, investigate the effect of statin use only at the baseline – ignoring possible changes in participants' health state, habits and, therefore, drug consumption which might have occurred during the more than 6 years of follow-up. According to unpublished data for up to 2008 from QResearch, and particularly relating to the older population, use of statins was growing during the study years so doctors might have started prescribing statins simply because they had been convinced of their benefits. Similar trends were observed in a Danish study, which also noted a decrease in use for 2009 (Wallach Kildemoes 2012, Health Policy, 108, 216-27). This information might be taken into account by applying the Cox model with time-dependent covariates and so increase the credibility of the results. Did the authors consider it? If not, the reasons should be discussed. According to the description of the study in ref. 19, the first

follow-up clinical visit was to be funded. Did the authors run any comparative analysis (e.g. sensitivity) based on this first follow-up visit? Again, any reason for not doing so should perhaps be mentioned.

We thank the reviewer for raising this point. The CHAMP study participants were interviewed at baseline and at two years. Five year follow-up assessments are yet to be completed this year.

We agree that it would be interesting to investigate the implications of change in statin use over time. However, at the time of these analyses medication data from Year 2 follow-up was not available. We have addressed this (also raised by Reviewer 1), and added the following text (page 21):

Moreover, it is unknown whether statins were stopped, started or the dose was changed during the follow-up.

7) As the authors note in the discussion there are no studies investigating the association between statin use and institutionalisation. But nothing is said about studies looking at the association between mortality and statin use. There are observational studies based not on general population data but on particular groups from a general population with common old age conditions. These should be mentioned in Discussion.

Thank you. We have addressed this and added a reference in relation to statins and mortality (pages 19-20).

In relation to statins and mortality, among older people with diabetes living in the community, statin use has been associated with reduced risk of cardiovascular and all-cause mortality.

Reviewer 3: Beatrice A Golomb MD, PhD
University of California San Diego, Medicine

The study addresses a very important issue. The important findings should be better highlighted, and placed better into context of existing literature. You might consider emphasizing institutionalization, the element that has not been looked at in the elderly, and using the mortality findings as a comparator to available RCT data to identify potential net direction of bias.

Thank you. We have now highlighted findings in relation to institutionalisation (also suggested by other reviewer 1 and 2) and have compared the mortality findings to RCT and observational data (pages 19-20).

1) Major issues:
Central Findings
a. It is unclear why the vital finding that medium and high dose statin users had significantly increased rates of institutionalization is buried (not mentioned in abstract or conclusions). In

general, healthy user/ healthy tolerator effects of statins have shown greater spurious advantages with high dose statin use (not supported in head to head higher vs lower dose comparisons in RCTs, even in stable CAD)[Golomb, 2009 #54142].

Thank you for raising this issue. These findings are not emphasised as they were not statistically significant in the propensity score adjusted model. Therefore, we believe it would be misleading to say that in this study use of high dose statins was related to increased risk of institutionalisation.

We have added the following statement in the discussion section (page 19):

Interestingly, high dose statin users had a hazard ratio of 2.45 (95% CI: 1.12, 5.33) for increased risk of institutionalisation. However, this association was not significant in the propensity score adjusted model.

2) It is emphasized (1st sentence of discussion) that "The objective of this cohort analysis was to evaluate the relationship between statins and two clinically important outcomes, institutionalisation and death in older men, accounting for frailty." It was also stated that elderly respond worse to drugs – i.e. frailty is a potential effect modifier. Given these, an anaysis stratified on frailty is the most sensible.

Thank you. Please see comments below.

3) A range of analyses comparing frail on statin to nonfrail not on statin (which are uninterpretable) are included; while the hazard ratio and CI comparing frail on-statin to frail not on statin is not. This analysis is central to the purpose of the study. (It appears, from dividing taking the ratio of HRs relative to healthy not-on-statin persons, that the HR for institutionalization with statins, among frail individuals, would be about 2.1) Relation of statin use to institutionalization in frail elderly is important to frail elderly, whether or not the frailty x statin interaction achieves significance here.

As stated on page 14, we stratified participants based on frailty status and statin use as robust or pre-frail not on statins; robust or pre-frail on statins; frail not on statins and frail on statins. Robust or pre-frail participants are referred as "non-frail" in the analysis. Moreover, non-frail not on statins were assigned as the reference group for the subgroup analysis.

As the interaction term between frailty and statins was not statistically significant, we could not state that frail men on statins had higher risk of institutionalisation than frail men not on statins. However, we did state that frailty was a significant predictor of institutionalisation, regardless of mediation exposure (page 20).

We have also added the following text on page 20:

Even though there was no significant interaction between statin use and frailty on institutionalisation rates, frail men using statins had twice the risk of institutionalisation as frail men not using statins.

4) Healthy User Effects: The study design bears the expected major limitation for cohort studies of preventive medications. You correctly mention that users are more likely to have CAD (which may be controlled for – or stratified on). Healthy user bias is alluded to briefly, but the power of this effect in observational studies of preventive medications is powerful: this led HRT to appear to have strikingly large and significant benefits to incident dementia and CVD. Subsequent randomized trials, ensuring against systematic differences between HRT users and nonusers (other than HRT use), showed the causal effect of HRT was modest but significant increase in these outcomes. Etc. Similar problems have arisen flu vaccine and statin trials. An editorial in BMJ has reviewed the foundations for these forms of bias in relation to statin use (including healthy tolerator effects, also strongly germane here)[Golomb, 2011 #67608]. Though it is alluded to in the discussion, this limitation might be more explicitly acknowledged as a potential large force.

Thank you for this comment. We have now discussed the implications of healthy user effects and healthy tolerator effects (comment 8), and have also added the suggested reference (page 21).

The implications of healthy user bias (eg. unhealthy individuals will be less likely to use statins, which may indicate benefits of statins in observational studies) and healthy tolerator bias (eg. adherence to preventative drugs including statins is associated with better outcomes in general) should be also considered.

Management of other forms of bias and confounding:
a. Covariates/ confounders vs mediators
“Other medical conditions included: diabetes, thyroid dysfunction, osteoporosis, Paget's disease, stroke (cause), Parkinson's disease (consequence), epilepsy, intermittent claudication (Cause), chronic obstructive lung disease, liver disease, chronic kidney disease or renal failure, cancer (excluding non-melanoma skin cancers), or arthritis. The number of reported comorbidities was dichotomised at the upper quartile (≤1 versus ≥2). Data on body mass index (BMI; kg/m2) was obtained. Multiple medication use or polypharmacy was defined as the use of ≥5 regular prescription medicines”

Comment: Several of these may be caused by statins* and serve as mediators of mortality, or correlate with processes that are involved in mediation. Adjusting for potential mediators (or for factors correlated with and thus collinear with such mediators) may “adjust out” a true association. At the very minimum, this should be characterized as a limitation of the study.
** diabetes (particularly in elderly), cancer (RCT evidence is exclusively in elderly), liver disease, kidney disease, presumed “intermittent claudication” as a manifestation of statin exercise intolerance (I was involved in care of a patient with documented PAD (ABI ~0.6 bilaterally) and presumed IC manifested by months of severe calf pain with ambulation arising at < 1 block, who had been pre-opped and was scheduled for vascular surgery. He stopped his statin prior to the surgery and the symptoms calf pain with ambulation fully resolved, with no restriction in ambulation, and did not recur (he remained off statins).}

5) A number of the health variables that have been adjusted are outcomes to which statin use can predispose, particularly in elderly. {These include diabetes (particularly in elderly)[Sattar, 2010

#56915][Golomb, 2012 #67719]. higher BMI, neurodegenerative disease, cancer (in elderly exclusively[Shepherd, 2002 #4295].), renal and liver disease.} An adjustment approach that includes adjustment for potential mediators, or factors correlated to mediators, is problematic, it may "adjust out" a true relationship.

Similarly, statins can promote polypharmacy to treat adverse effects, which may be mediators in statin induced death and institutionalization. (I had a striking recent case of a patient who was out of town for six months, during which a doctor initiated statins, which led to a cascade of problems, causing the patient to be placed on more medications for problems, and to develop more problems from the medications. These all resolved when I stopped the set of six or seven added medications.) There is not a foolproof way of addressing these, because these problems can also arise in absence of statin use, and in that fraction adjustment would be beneficial.

Thank you for these points. While a number of covariates we adjusted our analysis for may be associated with statin use, they are also important risk factors for the clinical outcomes investigated in our analysis. We believe it is appropriate to include all the covariates in our analysis. However, we have now added the following statement in the study limitations section (page 21):

While some covariates adjusted for in our analysis may be potential mediators of statin use, they are also important risk factors for the clinical outcomes investigated in our analysis.
6) Healthy tolerator bias: some who are not on statins may select into the nonuser group via statin intolerance – which may be tied to lower vigor (e.g. greater mitochondrial dysfunction[Golomb, 2008 #51302]), which may predict worse outcomes. It may also lead to loss of evidence of dose effects (higher doses are more likely to lead to discontinuation, and further boosting of lower vigor participants into the nonuser group

Recommendation: This limitation should be acknowledged.

We have addressed this, as per comment 4 (please see page 21).

Power:
7) Bias and confounding add significant uncertainty to how meaningful the point estimates are. But supposing they were presumed credible, effects of the observed magnitude (particularly for institutionalization) would be important to identify. Failure for effects of this magnitude to provide significance emphasizes that the study is underpowered. (It should probably not be characterized as a large study: for a cohort study, it is rather small.)

Thank you. We have now pointed out that "larger studies" are need to confirm these findings (page 19).

Statements needing revision: Finally, a number of statements and characterizations are in need of correction or revision

a. Introduction: "While the data from published RCTs and prospective studies indicate that statins reduce the incidence of cardiovascular events and all-cause mortality there are still significant gaps

in evidence on the safety of statins in a real-world setting."

8) Comment: There was NOT reduction in all-cause mortality in the only randomized trial focused on the elderly (the PROSPER trial)[Shepherd, 2002 #4295]. Nor was there even a trend to mortality benefit with statins relative to placebo (odds ratio approximating 1.0), though this was a high-CVD risk sample, with heart disease or risk factors beyond high cholesterol – a sample far more likely a priori to experience mortality benefit than the sample here, with greater expected statin benefits and fewer expected harms. Moreover, that trial showed a statistically significant 25% increase in incident cancer[Shepherd, 2002 #4295] (a finding that was elsewhere shown to be modified significantly with age, and which is completely absent in samples of middle aged subjects, and meta-analyses of these. Papers reviewing separate risk-benefit considerations of statin use in elderly are available [Golomb, 2005 #9692].

Thank you. We have corrected this statement, and added a sentence regarding the findings of the PROSPER trial in the discussion section (page 20).

In contrast, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial data demonstrates benefits in reducing the risks of coronary diseases, however there are no benefits in overall mortality.

9) Statement under "Article focus": "There is limited data in relation to statin use and clinical outcomes in representative populations of community-dwelling older people."
Comment: This implies these are data in "representative populations of community-dwelling older people." BMJ Open just published a study showing that elderly who participate in studies are healthier [Golomb, 2012 #77145]. Subjects here were already participants in a program, who are expected to have been healthier than their age-sex matched compatriots, at least at the time of initial entry, a limitation that should be acknowledged, at least by indicating. There is little cause to presume this sample is much more representative than the clinical trial sample in PROSPER, which has the advantages of randomization and larger sample size[Shepherd, 2002 #4295].

Thank you. We have addressed the representativeness issue in the recruitment bias section (page 21). Interestingly, the response rate in the CHAMP study is similar to other comparable cohort studies of this type, and the use of statins in the CHAMP study (42.9%) was very similar to a random sample of older Australians aged ≥75 (43.0%).

10) Statement under "Key messages": "The findings of this prospective cohort study imply no independent association between statin use and institutionalisation or death in community-dwelling older men."

Comment: "Imply no independent association" implies absence of an independent association. The findings do not do this. They suggest the possibility of a sizable link to institutionalization, particularly in frail elderly, despite potential sources of confounding most of which will work against an association, but the study is underpowered to demonstrate significance. (A more correct statement is that the findings indicate need for further study, but can neither affirm nor exclude an

important, sizeable effect on institutionalization.) The trend to lower HR for death in statin users is well within the range that may be ascribed to healthy user / healthy tolerator effects noted above. But the findings for institutionalization are both sizeable and opposed in direction to expected healthy user effects. The HR for institutionalization for statin users was 2.1 fold greater than for nonstatin users (4.3 / 2.07) = 2.1. Doubling in the risk of institutionalization, if affirmed in a larger study, would be an extraordinarily important finding. This has serious prospects to be real, given randomized data showing fatigue (which you cite), increased glucose problems which have been found to be markedly stronger in trials with more older participants[Sattar, 2010 #56915]; and within trials, among subjects of older age within the elderly age group[Golomb, 2012 #67719]. (Diabetes will in turn lead to prospects for mortality and disability, and also to more medications with their own prospects for morbidity), increased weakness in elderly (in RCT settings).
Recommendation: The statement should to be revised. The text should make clear that a) no significant finding was observed (absence of significance is not evidence of absence in the setting of a large hazard ratio); b) that well documented healthy user effects, documented for numerous preventive medications (flu vaccine, HRT) extending to statins could lead to bias in a favorable direction; c) that if the observed point estimate, of a doubling in risk of institutionalization among frail persons (and a 40% increase among others) is real, it would be important to demonstrate, or refute, in subsequent study.

Thank you. We have now amended statements under “Key messages” and abstract conclusion section, as suggested in point a) above. Point b) and c) have been addressed in responses to previous comments.

11) Statement: “Randomised trials in frail and robust older people with clinically relevant endpoints are required to inform therapy in this population”
Reviewer Comment: Such study in (generally) robust elderly – i.e. the elderly that are generally able to participate in studies[Golomb, 2012 #77145] -- already showed no (trend toward) mortality or serious morbidity benefit, complete loss of the stroke benefit seen in younger age, and a statistically significant increase in incident cancer. Institutionalization has not been examined, but the available evidence does not provide significant support for use of statins in elderly, even if robust providing lower prospects for harm, and at higher than typical prospects for benefit (with (stable) CAD).
Frail elderly inherently don’t tend to show up for studies [Golomb, 2012 #77145]. Cognitive limitations (which also affect compliance), physical frailty, transportation obstacles, and vigor all likely play roles. If some were to qualify by some definition of frailty, they would likely still be highly different from the frail group they are intended to reflect

Recommendation: Be clear what exactly you want these randomized trials to do, that a) they are capable of doing (so, frail elderly unlikely to be able to participate in a RCT); and b) have not already done.

Thank you. We have amended this statement to state:

Randomised trials utilising operational frailty definitions with clinically relevant endpoints are required to inform therapy in this population.

Under “Strengths and limitations of this study”
e. Far more important than either the first statement (saying this is a large study -- which for a population cohort it is not); or the 2nd focusing on geography, is the limitation that this study is underpowered even to show significance of a doubling in institutionalization among the frail group, and a 40% increase in the healthy group.

Thank you. We have deleted the word “large” in the first statement, and have replaced the second statement to include the following comment (page 7):

The study may have been underpowered to demonstrate the statistical significance in relation to statin use and institutionalisation.

12) “the possibility of confounding by indication and unmeasured confounders cannot be excluded.” In addition to confounding by indication and by “unmeasured” confounders, is the influence of measured variables for which adjustment may adjust out mediating mechanisms. I would rephrase this limitation and perhaps emphasize that observational studies of preventive medication users, including statins, have often been biased by healthy user and healthy tolerator bias [Golomb, 2011 #67608].

Thank you. We have corrected this statement, and added a comment regarding healthy user and healthy tolerator bias (page 7):

Observational studies of preventative medication users, including statins, are often biased by healthy user and healthy tolerator bias.

Introduction
g. However, it is not clear how the findings of these trials translate to clinically significant outcomes in general populations of older people. This may be because the representation and representativeness of older people in published RCTs of statins is generally poor.5

13) Comment: You are the one drawing the inference that it is not clear how findings of trials translate, from which the readers infer that you have a reason. Therefore it isn’t meaningful to say “This may be because”.

We have deleted “This may be because” and have now stated the following:

However, it is not clear how the findings of these trials translate to clinically significant outcomes in general populations of older people, as the representation and representativeness of older people in published RCTs of statins is generally poor.

(Representativeness of others’ criticized: should acknowledge limitations in representativeness here.)

14) Competency:
Statement: All participants were screened for cognitive impairment, and those who tested positive underwent full neuropsychological assessment. Participants were classified as cognitively impaired if they were diagnosed with either dementia or mild cognitive impairment"

Query: Were they administered MacArthur competency testing or some other procedure, to ensure those who were cognitively impaired had competency to consent?

Participants were screened for cognitive impairment using the Mini Mental State Examination (MMSE) and the Informant Questionnaire on Cognitive Decline (IQCODE) during the baseline clinic assessment. In addition to the cognitive screen participants also completed other cognitive assessments including Addenbrooke's Cognitive Examination, Trail Making Task B, Weigl-Colour Form Sorting test and Logical Memory Recall test. Participants with a MMSE less than or equal to 26 and/or IQCODE greater than 3.6 were invited to have detailed clinical assessments by the study geriatrician. This assessment included a review of medical comorbidities and medications, a standardized neurological assessment, a more detailed informant interview and the Rowland Universal Dementia Assessment Scale (RUDAS). At a weekly consensus meeting two geriatricians, a neurologist and a neuropsychologist reviewed all medical, cognitive, informant and functional data and reached a final diagnosis of cognitive status for each participant. At the end of the screening and clinical assessments, participants were categorized as having dementia (n= 93), mild cognitive impairment (n = 120), unknown cognitive status (n= 164) or cognitively intact (n= 1328). We have published this, and we did cite the paper (reference number 24) in the manuscript.

For those men that were cognitively impaired, consent from next of kin was obtained.

15) Prior Statin Use
How was prior statin use handled? Adverse effects of statins on muscle, neuropathy, and cognition can have lingering pathological and sometimes clinical effects; failure to address this can produce bias to the null, for effects that are adverse.

As we have stated on page 21, we were unable to differentiate former users from non-statin users.

16) Citation needed:
Frail individuals are more likely to use more medicines,10 and are at increased risk of adverse effects from medicines."
Comment: This is a major reason behind your stratified analysis, a citation should be provided.

Thank you. We have referenced this statement (please see page 9).

17) Clarification needed:
Statement: "Participants were asked whether they had taken any subsidised prescription or non-prescription medications during the past month."
Clarification sought:: Why just subsidized medications?

Data on all prescription and non-prescription medications was collected, and used in this analysis.

We have deleted “subsidised” to avoid confusion.

18) Clarification needed:
“Data on the duration of statin use (years) were obtained”
How? If you could obtain duration, you could obtain prior statin use

Unfortunately we could not obtain data on prior statin use. During the clinic visit, men were asked how long they have been taking their current medications for, including statins. However, men that reported no exposure to specific drugs or drug classes, including statins were not asked whether they were prior users of specific drugs.

19) Clarification needed:
What was the average follow-up period? You mention the maximum follow-up of ~6.8 years.

The average follow-up period was 4.0 years. We have now stated this on page 12.

20) Clarification needed:
“Statistical Analysis: Data are summarised as means (standard deviations) or counts (proportions). Differences between statin users and non-users were compared using the non-parametric or $\chi 2$-tests as appropriate…”
Comment: Presumably you are referring to covariates rather than outcomes: if so, so clarify.

Yes, that is correct. We have clarified this (page 14).

21) Clarification needed:
“We then conducted the Cox proportional hazards regression models for the effects of statins on institutionalisation and death, adjusted for all potential confounding factors at baseline.”
Please clarify the exact list of variables that were adjusted and how each were defined/ rated.

We have added the list of covariates as suggested (page 15). The covariates are defined on pages 13-14.

We then conducted the Cox proportional hazards regression models for the effects of statins on institutionalisation and death, adjusted for all potential confounding factors at baseline including age, education, marital status, alcohol use, smoking, BMI, self-reported comorbidities, self-reported cardiovascular diseases, impaired vision, depression, cognitive impairment, functional status, self-rated health, polypharmacy, total cholesterol, high density lipoprotein cholesterol and triglyceride concentrations.

22) Important statement:
“It is unknown whether medicines do more good than harm in older adults with established geriatric syndromes.”
This is an important comment, but I wonder if you may wish to qualify if (e.g., preventive medications). “harm” and “good” may be unclearly defined, and medicines that reduce suffering may be considered by some to clearly do good (even if they were to increase mortality)

Thank you. We believe this statement encompasses all of the insights and interpretations raised.

23) Discussion
“These findings suggest that statins in frail older men may not reduce the risk of institutionalisation or death.” In fact, your study found an increase in institutionalization, particularly with higher statin doses.

As per our previous response (comment 1), the propensity score analysis does not support the increase in institutionalisation rates. We believe it would be inaccurate to state that high dose statin use is associated with an increase in institutionalisation in our study sample.

24) Strengths section
“ good quality medication and outcome data”
In what way are the medication data good quality? They aren’t from an electronic database; and you don’t seem to address prior statin use…

The recording of actual drug use was based on inspection of all drugs brought by the men during a clinic visit. This gives more accurate information on drug exposure in Australia than does information obtained from databases, medical records, pharmacy records, or subject questionnaires or interviews.

We have added the following statement (page 20):

A careful and systematic medication inventory was performed by checking all medications brought in by the men during a clinic visit.

“ and adjustment for a number of covariates related to the risk of institutionalisation and death.”
Unfortunately, some may be in the causal pathway.

We have addressed this, as per comment five.

The propensity score is problematic due to the cause/ covariate/ confounder/ mediator issue that affects a number of the covariates.

The mediator issue has been addressed, as per comment five.

25) “In relation to statin exposure, non-users group may include former users of statins.”
That nontolerators may be unhealthier and disproportionately populate the nonuser group with sick people is especially likely to be a big factor among elderly.

Thank you. Healthy tolerator bias has been addressed, as per comment 12.

26) Concluding paragraph
“In this prospective observational study, use of statins was not associated with increased risk of

institutionalisation or death. However, in this sample, frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure."

The latter sentence is both unrelated to the described intent of the study and is a "duh". Why is this statement included, but the study-relevant finding of significant increased institutionalization among those on higher statin doses not mentioned here?* Why is the doubling of institutionalization for statin users, among frail elderly, not mentioned here (or in the results)?
*"Medium (HR=2.00; 95%CI: 1.02 to 3.93) and high (HR=2.45; 95%CI: 1.12 to 5.33) dose statin users were significantly more likely to be institutionalised when compared to those not taking statins."

We believe these statements are appropriate, and are supported by the analysis. Since the propensity score adjusted models did not demonstrate the statistically significant findings, we feel it would be inaccurate to state that high dose statin use is associated with increased risk of institutionalisation. We have clarified the issues around statistical significance (page 22).

"In this prospective observational study, use of statins was not associated with a significantly increased risk of institutionalisation or death. However, in this sample, frail men were more likely to be institutionalised and die than non-frail men, independent of their statin exposure."

VERSION 2 – REVIEW

REVIEWER	Arduino A Mangoni, Professor of Clinical Pharmacology, Flinders University, Adelaide, Australia. No competing interests.
REVIEW RETURNED	31-Jan-2013

- The reviewer completed the checklist but made no further comments.